REMARKS

Claim status. Claims 17 to 25, 39 to 42, and 62 to 65 are pending. With the present amendment, the Applicants have canceled Claim 1, amended Claims 17 and 19, and added Claims 62 to 65. These amendments are supported in the specification as described below.

Rejection under 35 U.S.C. Section 112. The Examiner objects to the scope of the claims, stating that the specification "fails to disclose combination treatments with any species or variant of OPG. Furthermore, the specification does not disclose methods for treating a particular condition leading to bone loss. The specification discloses methods for specifically treating bone loss not the condition." (Office Action at page 5). The Examiner further objected that the meaning of the term "OPG protein" was unclear. The Examiner also objected to the scope of variants included within the term "OPG protein."

Although the Applicants do not believe any undue burden of experimentation existed with the claims in their prior form, the present form of Claim 17 obviates any of the Examiner's concerns regarding experimentation with variants of OPG or with the meaning of the term "OPG protein."

In the interest of furthering prosecution, the Applicants have added new claims 62 to 65. Claim 62 is supported by Figures 9E and 9F; page 8, lines 27-28; page 15, lines 10-12; page 19, lines 25-34; and Table 3, page 157. Claim 63 is supported in the specification by Figures 9A and 9B; page 8, lines 23-24; page 15, lines 13 and 14; and page 157, line 9. Claim 64 is supported by Figures 9C and 9D; page 8, lines 25-26; page 15, lines 13 and 14; page 19, lines 25-34; and Table 3, page 157. Claim 65 is supported in the specification by page 15, lines 3-8.

Regarding the Examiner's comments on conditions leading to bone loss, the specification describes many such conditions. The Applicants believe the Examiner's objection is to the term "conditions" and so have amended the claim to avoid use of the term.

The Applicants contend that the Examiner's objection to Claims 19 and 21 have been obviated by the amendment to Claim 19.

With regard to the objection to Claim 24, the Applicants wish to point out that "etanercept" is known in the art to be the generic name for the well known pharmaceutical marketed under the trade name Enbrel® (see enclosure). Accordingly, no amendment of Claim 24 is necessary.

Rejection as double patenting. The Examiner's various obviousness-type double patenting rejections all rely on U.S. Pat. No. 6,288,032 ("the '032 patent"). The '032 patent issued from a parent application for the present application. To address this ground of rejection, the Applicants submit herewith a terminal disclaimer over the '032 patent.

Formal amendments. The remaining amendments correct cross-references to figure numbers. Persons of ordinary skill in the art would have understood the amended references from their context in the specification.

Conclusion. In light of the foregoing amendments and remarks, the Applicants respectfully request entry of all amendments, withdrawal of all objections and rejections, and allowance of all claims.

Respectfully submitted,

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Date: October 2, 2002

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One Amgen Center Drive
Thousand Oaks, California 91320-1799

VERSION WITH MARKINGS TO SHOW CHANGES MADE

At page 5:

Figure 1. A. FASTA analysis of novel EST LORF. Shown is the deduced FRI-1 amino acid sequence aligned to the human TNFR-II sequence (SEQ ID NO: 169 and SEQ ID NO: 169a). B. Profile analysis of the novel EST LORF shown is the deduced FRI-1 amino acid sequence aligned to the TNFR-profile (SEQ ID NO: 170 and SEQ ID NO: 170a). C. Structural view of TNFR superfamily indicating region which is homologous to the novel FRI-1.

Figure 2. Structure and sequence of full length rat OPG gene, a novel member of the TNFR superfamily. A. Map of pMOB-B1.1 insert. Box indicates position of LORF within the cDNA sequence (bold line). Black box indicates signal peptide, and gray ellipses indicate position of cysteine-rich repeat sequences. B, C. Nucleic acid and protein sequence of the Rat OPG cDNA. The predicted signal peptide is underlined, and potential sites of N-linked glycosylation are indicated in bold, underlined letters (SEQ ID NO: 120 and 121). D, E. Pileup sequence comparison (Wisconsin GCG Package, Version 8.1) of OPG with other members of the TNFR superfamily, fas (SEQ ID NO:128); tnfr1 (SEQ ID NO: 129); sfu-t2 (SEQ ID NO:130); tnfr2 (SEQ ID NO:131); cd40 (SEQ ID NO:132); osteo (SEQ ID NO:133); ngfr (SEQ ID NO:134); ox40 (SEQ ID NO:135); 41bb (SEQ ID NO:136).

At page 8:

Figure 9. Structure and sequence of mouse and human OPG cDNA clones. A, B. Mouse cDNA and protein sequence (SEQ ID NO: 122 and 123). C, D. Human cDNA and protein sequence. The predicted signal peptides are underlined, and potential sites of N-linked glycosylation are indicated in bold (SEQ ID NO: 124 and 125). E, F. Sequence alignment and comparison of rat, mouse and human OPG amino acid sequences. Muosteo (SEQ ID NO: 171); ratosteo (SEQ ID NO: 172); huosteo (SEQ ID NO: 173).

Figure 10. Comparison of conserved sequences in extracellular domain of TNFR-I and human OPG. PrettyPlot (Wisconsin GCG Package, Version 8.1) of the TNFR1 and OPG alignment described in example 6. Top line, human TNFR1 sequences encoding domains 1-4 (SEQ ID NO: 126). Bottom line, human OPG sequences encoding domains 1-4. Conserved residues are highlighted by rectangular boxes (SEQ ID NO: 174).

At page 9:

Figure 12. Structure of OPG cysteine-rich domains. Alignment of the human (top line SEQ ID NO: ~~136~~139) and mouse (bottom line SEQ ID NO:175) OPG amino acid sequences highlighting the predicted domain structure of OPG. The polypeptide is divided into two halves; the N-terminus (A), and C-terminus (B). The N-terminal half is predicted to contain four cysteine rich domains (labeled 1-4). The predicted intrachain disulfide bonds are indicated by bold lines, labeled "SS1", "SS2", or "SS3". Tyrosine 28 and histidine 75 (underlined) are predicted to form an ionic

interaction. Those amino acids predicted to interact with an OPG ligand are indicated by bold dots above the appropriate residue. The cysteine residues located in the C-terminal half of OPG are indicated by rectangular boxes.

At page 13:

Figure 29A through 29G. Sequence of OPG-Fc. DNA and encoded protein sequences are shown. Restriction sites for various nucleases are noted above the DNA sequence (SEQ ID NO: 176 and 177).

CLAIMS:

17. (Amended) A method of treating bone loss, which comprises administering ~~The method of claim 1, wherein~~ an IL-1 inhibitor, a TNF-•inhibitor, and ~~the~~an OPG protein, wherein " OPG protein" refers to an antibody to OPG ligand or a polypeptide comprising conserved residues from residues 22 to 185 of SEQ ID NOS: 171, 172, and 173.~~are administered.~~

19. (Amended) The method of Claim 17, wherein the TNF-•inhibitor comprises sTNFR-I, sTNFR-II, sTNFR fragments, or sTNFR-Fc, wherein "sTNFR" refers to sTNFR-I or sTNFR-II.

NEW CLAIMS:

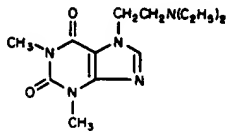
62. (new) The method of Claim 17, wherein the OPG protein comprises a sequence comprising the conserved residues from residues 22 to 185 of SEQ ID NOS: 171, 172, and 173.

63. (new) The method of Claim 17, wherein the OPG protein comprises residues 22 to 185 of SEQ ID NO: 123.

64. (new) The method of Claim 17, wherein the OPG protein comprises residues 22 to 185 of SEQ ID NO: 125.

65. (new) The method of Claim 17, wherein the OPG protein comprises an antibody to OPG ligand.

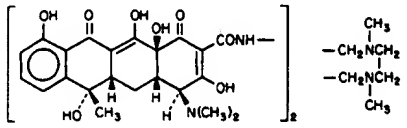
Etamiphyllin. $C_{13}H_{21}N_5O_2$. 279.34. [Etamiphylline is BAN.] 7-(2-Diethylaminoethyl)theophylline. *CAS-314-35-2.* INN; MI.



Etamiphyllin Methesculetol — *See* Metescufylline.

Etamivan (INN; BAN; DCF) — *See* Ethamivan.

Etamocycline. $C_{50}H_{60}N_6O_{16}$. 1001.04. *N,N,*-{Ethylenebis [(methylimino)methylene]}bis-[4′-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide]. *CAS-15590-00-8.* INN; DCF.

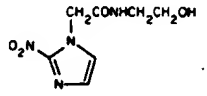


Etamsylate (INN; BAN; JAN) — *See* Ethamsylate.

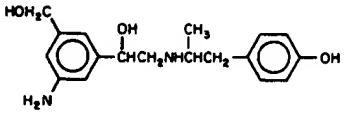
Etanercept *[1998]* (et a ner' sept). $C_{2224}H_{3472}N_{618}O_{701}S_{36}$ (monomer). 51,238 daltons (non-glycosylated protein, monomer). 1-235-Tumor necrosis factor receptor (human) fusion protein with 236-467-immunoglobulin G1 (human γ1-chain Fc fragment), dimer. *CAS-185243-69-0.* INN. *To decrease signs and symptoms of rheumatoid arthritis.* Enbrel (Immunex) ✧*rhu TNFR:Fc*

LPQVAFTPY	APEPGSTCRL	REYYDQTAQM	CCSKCSPGQH	AKVFCTKTSD
TVCDSCEDST	YTQLWNWVPE	CLSCGSRCSS	DQVETQACTR	EQNRICTCRP
GWYCALSKQE	GCRLCAPLRK	CRPGFGVARP	GTETSDVVCK	PCAPGTFSNT
TSSTDICRPH	QICNVVAIPG	NASMDAVCTS	TSPTRSMAPG	AVHLPQPVST
RSQHTQPTPE	PSTAPSTSFL	LPMGPSPPAE	GSTGDEPKSC	DKTHTCPPCP
APELLGGPSV	FLFPPKPKDT	LMISRTPEVT	CVVVDVSHED	PEVKFNWYVD
GVEVHNAKTK	PREEQYNSTY	RVVSVLTVLH	QDWLNGKEYK	CKVSNKALPA
PIEKTISKAK	GQPREPQVYT	LPPSREEMTK	NQVSLTCLVK	GFYPSDIAVE
WESNGQPENN	YKTTPPVLDS	DGSFFLYSKL	TVDKSRWQQG	NVFSCSVMHE
ALHNHYTQKS	LSLSPGK			

Etanidazole *[1987]* (et a nyde' a zole). $C_7H_{10}N_4O_4$. 214.18. (1) 1*H*-Imidazole-1-acetamide, *N*-(2-hydroxyethyl)-2-nitro-; (2) *N*-(2-Hydroxyethyl)-2-nitroimidazole-1-acetamide. *CAS-22668-01-5.* INN. *Antineoplastic (hypoxic cell radiosensitizer).* Radinyl (Roberts Pharmaceutical) ✧*SR 2508; NSC-301467*

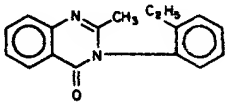


Etanterol. $C_{18}H_{24}N_2O_3$. 316.39. 5-Amino-α-[[(*p*-hydroxy-α-methylphenethyl)amino]methyl]-*m*-xylene-α,α′-diol. *CAS-93047-39-3.* INN.

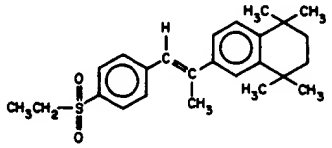


Etaperazine — *See* Perphenazine.

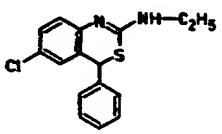
Etaqualone. $C_{17}H_{16}N_2O$. 264.32. 3-(*o*-Ethylphenyl)-2-methyl-4(3*H*)-quinazolinone. *CAS-7432-25-9.* INN; ML



Etarotene *[1990]* (e tar' oh teen). $C_{25}H_{32}O_2S$. 396.59. (1) Naphthalene, 6-[2-[4-(ethylsulfonyl)phenyl]-1-methylethenyl]-1,2,3,4-tetrahydro-1,1,4,4-tetramethyl-, (*E*)-; (2) 6-[(*E*)-*p*-(Ethylsulfonyl)-α-methylstyryl]-1,2,3,4-tetrahydronaphthalene. *CAS-87719-32-2.* INN. *Keratolytic.* (Hoffmann-LaRoche†) ✧*Ro 15-1570/000*



Etasuline. $C_{16}H_{15}ClN_2S$. 302.82. 6-Chloro-2-(ethylamino)-4-phenyl-4*H*-3,1-benzothiazine. *CAS-16781-39-8.* INN.



† Brand name formerly used, and/or firm no longer concerned with this product.